IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	SEAN B. CARROLL, Ph.D. *et al.*		
Serial No.:	10/662,918	Group No.:	1644
Filed:	09/15/03	Examiner:	Kim, Y.
Entitled:	**CLOSTRIDIAL TOXIN DISEASE THERAPY**		

SECOND DECLARATION OF DR. DOUGLAS C. STAFFORD UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Date: Oct. 26, 2007 By: Traci E. Light

Sir:

I, Douglas C. Stafford, under penalty of perjury, state that:

1. I was President and Chief Executive Officer of Ophidian Pharmaceuticals, Inc. at 5445 East Cheryl Parkway, Madison, WI 53711 ("Ophidian"). Ophidian was the original owner of the above-identified patent application.

2. I had supervisory responsibility for certain experimentation performed at Ophidian which has relevance to the subject matter in the above-referenced patent application. I have a Ph.D. degree in Immunology and was involved in the design and interpretation of studies described below. I previously supplied a 132 Declaration in this matter.

3. As noted in my prior Declaration, I have read U.S. Patent No. 4,748,018 cited by the Examiner. The '018 Patent teaches a method of passively immunizing a mammal against a condition caused by an antigen. The '018 Patent further teaches that inducing tolerance to such antibodies would enable passive immunization. The '018 patent states, "[t]his tolerance occurs in mammalian individuals who have been previously fed a material containing antibodies from the heterologous fowl species" (emphasis added). Accordingly, the examiner's statement that "the '018 patent teaches the tolerance is developed by the subsequent administration of antibody (col. 4, lines 42-45)" (emphasis added) is in an incorrect reading of the '018 patent.

4. It should be understood in the '018 patent that induction of tolerance is an active, deliberate process that requires administration "over time." The '018 inventors state, "the immune system tolerance, which is a necessary condition for heterologous antibody administration, does not occur naturally, and must be built up in a mammal subject **over time** by the feeding of material containing fowl antibodies." (emphasis added). Such time involves weeks to months. Indeed, the immunology literature is filled with such examples of deliberate induction of tolerance in animals (10-15 day tolerance regime in rats; Journal of Immunology, 1993, 151:5751) and humans (19 day tolerance regime in humans; Journal of Immunology, 1994, 152:4663). The '018 patent itself recites in its Example 2 that tolerance is induced in recipient rabbits by feeding antibody for "30 consecutive days prior to injecting [antibody]." They further go on to say, "[f]or older animals and humans, the minimum time to acquire tolerance can be up to several months." Such evidence makes it clear that tolerance will not be induced in merely a matter of hours. Thus, the multiple administrations in Example 6 to which the Examiner refers ("The mice received . . . treatments . . . 1 hour before and ½ hour, 4 hours, and 8 hours after botulinal toxin administration") will not induce tolerance. Clearly, there is no support for the Examiner's statement that the present invention "implicitly requires developing tolerance as well." Tolerance could not have been relevant given the rapid time course of the animal experiments.

5. Clearly, the teaching of the '018 patent is completely counter to the strategy used in the instant invention. Practice of the therapeutic regimen of the instant invention does not require the

prior, deliberate administration of heterologous antibodies and the induction of tolerance. Quite the contrary, the requirement for induction of tolerance (which might be expected to take several weeks to months) would be a rather impractical prerequisite for an acute treatment for microbial toxicity.

6. The Merck manual cited by the examiner does not describe an antitoxin for toxic shock. Furthermore, the Merck manual only describes the use of clostridial antitoxins to botulinum and tetanus toxins and both of these are parenteral therapies (requiring intramuscular, intracutaneous, or intravenous administration). The treatments described for *C. perfringens* infections include only chemical antibiotics such as penicillin G or tetracycline (in contrast to antibodies of the instant invention). Thus, this reference does not point to a passive, oral antibody therapy for *C. perfringens*.

7. The Uemura, et al., paper cited merely provides extant knowledge that *Clostridium perfringens* responsible for food poisoning produce entertoxin. Uemura does not teach toxic shock produced by clostridial species is treatable by antitoxin therapy. This simply cannot be found in the paper. Thus, this reference also does not point to a passive, oral antibody therapy for *C. perfringens*.

Dated: OCT 23, 2007

By: _____
Douglas C. Stafford, Ph.D.